

**REMARKS**

Claims 1, 5-11, and 13-16 are pending in the instant application. Claims 1, 5-11, and 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,574,495 to Golman et al. or United States Patent No. 6,278,893 to Ardenkjaer-Larsen et al. in view of either United States Patent No. 5,245,282 to Mugler et al. or United States Patent No. 6,310,478 to Heid. Reconsideration is respectfully requested.

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Applicants respectfully submit that the Office has failed to establish a prima facie case of obviousness of the present invention.

First, the Office states that

**“In response to applicant’s argument that they have solved a technical problem caused by a reduced signal due to an increased T2 relaxation rate of the imaging agent [sic.] the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.”**

The Office is mischaracterizing the Applicants arguments. The Applicants do not say that solving the technical problem of a reduction in T2 results from the invention, ie the Applicants are not citing this as a feature of the invention. The Applicants here are noting a deficiency in the prior art – that the fact that the T2 is decreasing is a hurdle which the present invention has overcome. The Office has it exactly backwards.

Additionally, in making the instant rejection, the Office states that “[t]he imaging agent in both Golman and Ardenkjaer et al will inherently exhibit variations in relaxation time T2 as a result of either physiological changes or metabolism in the sample.” Applicants respectfully submit that the reason the Office states that this variation in T2 is “inherent” is because neither reference outright says that this is what happens. In fact, there is no suggestion by Golman et al. or Ardenkjaer-Larsen that the MR imaging agent exhibits variations in relaxation time T2 as a result of physiological changes or as a result of e.g. metabolism or other physiological changes.

Furthermore, the Office concludes that it would have been obvious to substitute one known imaging sequence for another, as the results would have yielded predictable results. This conclusion is simply not supported. None of the cited references disclose that the MR imaging agents exhibit variations in T2 or that the sequences would have to be modified to account for these variations. Neither Mugler nor Heid disclose, teach, or suggest how to account for variations in T2 for the agent.

As previously noted, neither Mugler et al. nor Heid disclose a FISP pulse sequence which is used in MR imaging methods with a liquid imaging agent. The prior art discussion about FISP and steady state imaging is exclusively related to thermally polarised liquid compounds. The relationships that are true for thermally polarised liquid compounds are not applicable for hyperpolarised liquid compounds.

Moreover, the Office is incorrect to state that mere “substitution of one known type of fast pulse sequence for another would have yielded predictable results” is respectfully disputed by Applicants. There is a fundamental difference between different types of sequences. For instance, an EPI sequence flips the entire magnetization into the transverse plane. Thus, the optimization of EPI for the case of a hyperpolarized moiety would be entirely different from the optimization of a FISP sequence.

The fact is, then, that there is nothing predictable about the results. The technical problem solved by the instant invention was not understood in the prior art. Thus there is no suggestion in the prior art for solving it. Applicants again submit that the very realization that the flip angle has to be optimized in a different manner for the non-renewable magnetization is non-obvious, non-trivial, and distinguishes the present invention over prior art.

Applicants respectfully submit that the use of a pulse sequence which has only been used and optimized for thermally polarised liquid MR imaging agents would not be obvious to combine with the flip angles for hyperpolarised liquid compounds. Instead the instant

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invention realizes that by using such a FISP or PSIF sequence with a flip angle of 45 to 90 degrees, on a hyperpolarised imaging agent in liquid phase, a reduced signal (due to increased T<sub>2</sub> relaxation rate of the imaging agent) could be avoided. Thus, Applicants respectfully submit that any combination of the cited references by one of ordinary skill in the art would not achieve the instant invention. In view of the teachings of the prior art failing to disclose, teach, or suggest the instant invention, Applicants respectfully submit that the instant invention is patentably distinct over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

Therefore, as none of the cited references, either singly or taken together, disclose, teach, or suggest the instant invention, Applicants respectfully submit that the Office has failed to carry its burden to establish a prima facie case of obviousness. As such, the instant invention is patentably distinct over the prior art.

Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,

/Robert F. Chisholm/  
Robert F. Chisholm  
Reg. No. 39,939

GE Healthcare, Inc.  
101 Carnegie Center  
Princeton, NJ 08540  
Phone (609) 514-6905  
Fax (609) 514-6572